JOC*Article*

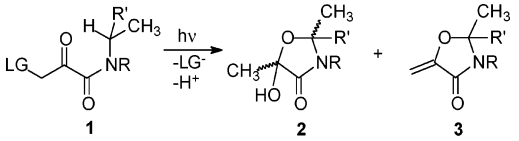
Photochemical Cleavage and Release of Carboxylic Acids from α-Keto Amides

Chicheng Ma, Mark G. Steinmetz,* Erica J. Kopatz, and Rajendra Rathore

Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53201-1881

mark.steinmetz@marquette.edu

Received February 7, 2005

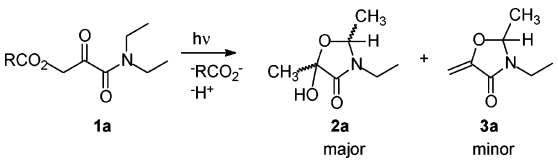


a (R = Et, R' = H)	94	:	6
b (R = iPr, R' = Me)	0	:	100
c (R = Ph, R' = H)	100	:	0

LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$, $C_6H_5CO_2^-$, 4-$NCC_6H_4CO_2^-$, $CH_3CONHCH_2CO_2^-$, BocAla, GABA, Glu

In aqueous media, α-keto amides $LGCH_2COCON(R)CH(R')CH_3$ (**1a**, R = Et, R′ = H; **1b**, R = ^{i}Pr, R′ = Me; **1c**, R = Ph, R′ = H) with various carboxylate leaving groups (LG) at the C-3 position undergo photocleavage and release of carboxylic acids with formation of diastereomeric 5-hydroxyoxazolidin-4-ones **2a**,**c** in the cases of **1a**,**c** or 5-methyleneoxazolidin-4-ones **3b** in the case of **1b**. For **1a**,**b**, Φ(photocleavage) = 0.24−0.38, whereas Φ(photocleavage) = ca. 0.05 for **1c**. The proposed mechanism involves transfer of hydrogen from an *N*-alkyl group to the keto oxygen to produce zwitterionic intermediates **4a**−**c** that eliminate carboxylate anions. The resultant imminium ions, $H_2C{=}C(OH)CON^+(R){=}C(R')CH_3$ **5a**−**c**, cyclize intramolecularly to **3b** or undergo intermolecular addition of water followed by tautomerization and cyclization to give **2a**,**c**. These inter- or intramolecular trapping reactions of **5** release protons that decrease the pH and cause bleaching of the 620 nm band of the pH indicator, bromocresol green. Determination of the bleaching kinetics by laser flash photolysis methods in the case of **1a** gives time constants of 18−137 μs, depending on the leaving group ability of the carboxylate anion, whereas amides **1b** show only a small leaving group effect. For **1a**, the large leaving group effect is consistent with rate-limiting carboxylate elimination from **4a**, whereas the proton release step would be largely rate determining for **1b**. Photolyses of **1a** (LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$) in neat CH_3CN results in carboxylate elimination to form imminium ion **5a**, followed by internal return to give aminals.

Recent studies have shown that α-keto amides **1a** undergo photochemical cleavage and release of carboxylate leaving groups (eq 1).[1] Photochemical elimination of substituted phenolate leaving groups has also been observed.[2]



(1)

These photoelimination reactions are highly efficient, the chemical yields of the released leaving groups are nearly quantitative, and carboxylate release occurs on the microsecond time scale.[3] Zwitterionic intermediates such as **4a** are thought to be involved in the eliminations. Analogous intermediates, generated photochemically via hydrogen transfer from an *N*-alkyl group to the keto oxygen, have often been proposed to account for the photorearrangement products of α-keto amides, which lack leaving groups.[4,5] The elimination of leaving groups

(1) Ma, C.; Steinmetz, M. G.; Cheng, Q.; Jayaraman, V. *Org. Lett.* **2003**, *5*, 71−74.

(2) Ma, C.; Steinmetz, M. G. *Org. Lett.* **2004**, *6*, 629−32.

(3) Ma, C.; Steinmetz, M. G.; Kopatz, E. J.; Rathore, R. *Tetrahedron Lett.* **2005**, *46*, 1045−1048.

(4) (a) Aoyama, H.; Sakamoto, M.; Kuwabara, K.; Yoshida, K.; Omote, Y. *J. Am. Chem. Soc.* **1983**, *105*, 1958−1964. (b) Aoyama, H.; Sakamoto, M.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1357−1359. (c) Aoyama, H.; Hasegawa, T.; Omote, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5343−5347. (d) Aoyama, H.; Hasegawa, T.; Watabe, M.; Shiraishi, H.; Omote, Y. *J. Org. Chem.* **1978**, *43*, 419−422.

10.1021/jo050246s CCC: $30.25
Published on Web 04/29/2005

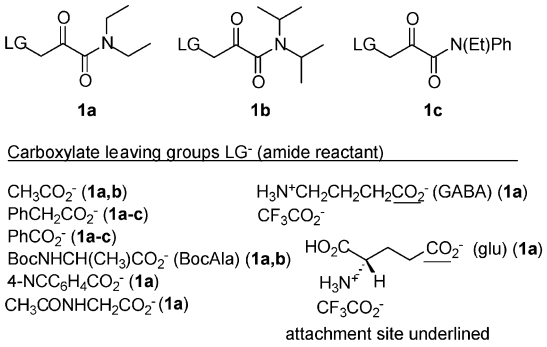
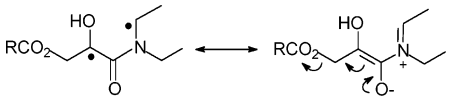


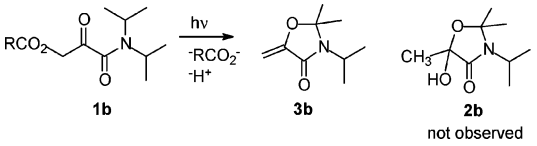
FIGURE 1. α-Keto amides **1a**−**c** and leaving groups LG^-.

from zwitterionic intermediates has warranted detailed studies, because it could serve as a mechanistic basis for developing a new class of photoremovable protecting groups and phototriggers ("cage compounds").[6,7]



4a

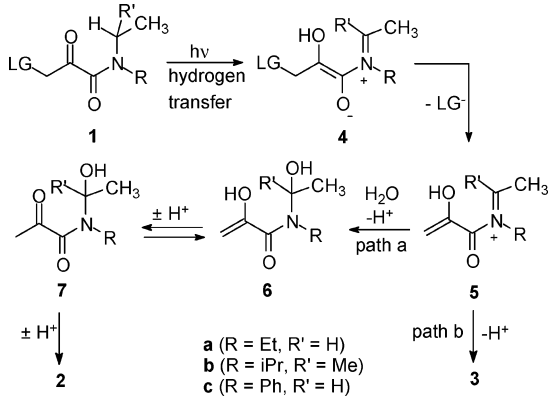
In this paper, we report full details of our photochemical studies of the photoelimination of a variety of carboxylate leaving groups (LG) from a series of *N*,*N*-diethyl α-keto amides **1a** (Figure 1). Comparisons are made to an analogous series of *N*,*N*-diisopropyl α-keto amides **1b** (Figure 1 and eq 2). Although the photocleavages of **1a** and **1b** appear to be similar, in the case of **1a** we find that the release rates are sensitive to the leaving group ability of the carboxylate groups, whereas only a small leaving group effect is observed for photolyses of **1b**. Furthermore, the photolytic eliminations of carboxylic acids from *N*,*N*-diethyl and *N*,*N*-diisopropyl α-keto amides **1a**,**b** are accompanied by the formation of different cleavage coproducts for the two amides. Hemiacetal **2a** is strongly favored in the case of **1a** (eq 1), whereas **3b** is exclusively formed from **1b** (eq 2). These observations point to some distinct differences in the mechanisms for formation of photoproducts from **1a**,**b**, which will be discussed in this paper.



(2)

The α-keto amide photocleavages require transfer of a hydrogen from an *N*-alkyl substituent to the oxygen of

SCHEME 1



the α-keto group. A number of mechanisms can be envisioned for the hydrogen transfer, including (1) hydrogen atom abstraction, (2) transfer of an electron followed by a proton,[5] and (3) net transfer of hydride (1,5-H shift). Although the hydrogen transfer mechanism is not well understood, previous studies[4c,5] have shown that when the carboxamide group favors an unreactive conformation with respect to hydrogen transfer, then the photochemistry is inefficient. The carboxylate photoeliminations are no different in this regard. Low quantum yields are found for the *N*-ethyl-*N*-phenyl amides **1c** (LG = $PhCO_2^-$ and $PhCH_2CO_2^-$) (Figure 1), which otherwise give similar photoproducts as **1a**.

We recently determined the rate constants for release of carboxylate groups from **1a** by a pH jump method that used laser flash photolysis.[3] In this paper, we report complete results of this study and additional results for **1b**. When α-keto amides **1a**,**b** are photolyzed, carboxylate anions and protons are released. The pH of the unbuffered aqueous medium decreases, which causes a change in the color of a pH indicator. The kinetics for the color change (bleaching) due to the released protons can be determined on the microsecond time scale by laser flash photolysis techniques (pH jump method).[8] Establishing the relationship between proton release rates and carboxylate anion release rates requires detailed knowledge of the mechanism, which for purposes of discussion is taken to be that depicted in Scheme 1. The proton release being monitored by the pH jump method is thought to occur after carboxylate elimination from zwitterionic intermediate **4** and would occur either via intermolecular addition of water to imminium ion **5** (path a) to ultimately give **2** or via intramolecular cyclization of **5** to give **3** (path b). These proton release rates would be subject to effects governing rates of carboxylate elimination, depending on which step is rate determining, the carboxylate elimination step, or the steps involving paths a or b.

Results

Synthesis of α-Keto Amides 1a−c. In the syntheses of **1a**−**c** (Scheme 2), ethereal suspensions of dry potas-

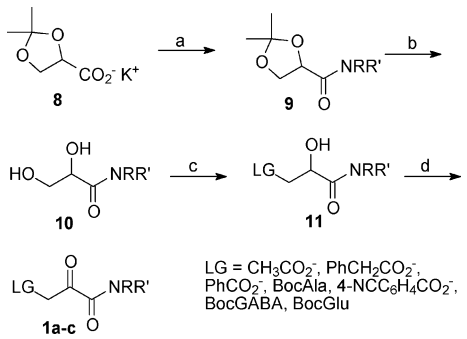
(5) Chesta, C. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 2188−2197.

(6) (a) Marriott, G., Ed. *Methods in Enzymology*; Academic Press: San Diego, 1998; Vol. 291. (b) Kahl, J. D.; Greenberg, M. M. *J. Am. Chem. Soc.* **1999**, *121*, 597−604. (c) Pirrung, M. C.; Fallon, L.; Lever, D. C.; Shuey, S. W. *J. Org. Chem.* **1996**, *61*, 2129−2136. (d) Lloyd-Williams, P.; Albericio, F.; Giralt, E. *Tetrahedron* **1993**, *49*, 11065−11133.

(7) (a) Morrison, J.; Wan, P.; Corrie, J. E. T.; Papageorgiou, G. *Photochem. Photobiol. Sci.* **2002**, *1*, 960−969. (b) Givens, R. S.; Lee, J.-I. *J. Photosci.* **2003**, *10*, 37−48. (c) Rajesh, C. S.; Givens, R. S.; Wirz, J. *J. Am. Chem. Soc.* **2000**, *122*, 611−618. (d) Cheng, Q.; Steinmetz, M. G.; Jayaraman, V. *J. Am. Chem. Soc.* **2002**, *124*, 7676−7677. (e) Corrie, J. E. T.; Barth, A.; Munasinghe, V. R. N.; Trentham, D. R.; Hutter, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 8546−8554.

(8) (a) Barth, A.; Corrie, J. E. T. *Biophys. J.* **2002**, *83*, 2864−2871. (b) Choi, J.; Hirota, N.; Terazima, M. *J. Phys. Chem.* **2001**, *105*, 12−18. (c) Viappiani, C.; Bonetti, G.; Carcelli, M.; Ferrari, F.; Sternieri, A. *Rev. Sci. Instrum.* **1998**, *69*, 270−276. (d) Walker, J. W.; Reid, G. P.; McCray, J. A.; Trentham, D. R. *J. Am. Chem. Soc.* **1988**, *110*, 7170−7177. (e) Gutman, M.; Huppert, D.; Pines, E. *J. Am. Chem. Soc.* **1981**, *103*, 3709−3713. (f) Clark, J. H.; Shapiro, S. L.; Campillo, A. J.; Winn, K. R. *J. Am. Chem. Soc.* **1979**, *101*, 746−748.

SCHEME 2[a]



[a] Conditions: (a) $(COCl)_2$, CH_2Cl_2; HNRR′, Et_3N. (b) Aq HOAc. (c) Acylation methods, see text. (d) PCC, CH_2Cl_2.

sium salt **8**[9] were converted to the acid chloride using oxalyl chloride, which was reacted with diethylamine, diisopropylamine, or *N*-ethyl-*N*-phenylamine in the presence of Et_3N to obtain amides **9a**−**c** in 65−70% yields. Deprotection of the vicinal diols **10** in ca. 90% yield was effected by refluxing with 70% aqueous acetic acid. The carboxylate leaving groups were then introduced in 60−85% yields by acylation of diols **10** using the corresponding acid chlorides in the presence of triethylamine at 0 °C (LG = $PhCO_2^-$, $PhCH_2CO_2^-$, 4-$NCC_6H_4CO_2^-$) or acetic anhydride at room temperature (LG = $CH_3CO_2^-$) or by DCC coupling of the carboxylic acids with catalytic DMAP (LG = BocGABA, BocGlu, BocAla). After chromatographic purification of the monoacylated products **11**, PCC oxidation of the secondary alcohols furnished the carboxylate-substituted α-keto amides **1a**−**c** in 80−85% yields. At 16.8 °C, compound **1c** (LG = $PhCH_2CO_2^-$) appeared to be an 8:1 mixture of conformers with respect to rotation about the O=C−N carboxamide bond, according to ^{1}H NMR integration of signals of the O−CH_2 group at δ 5.16 and 5.37.

The BocGABA derivatives of **1a**,**b** and BocGlu derivative of **1a** were deprotected in ca. 85% yields by treatment with CF_3CO_2H in CH_2Cl_2 at room temperature and purified on Sephadex LH-20. For **1a** (LG = Glu), further purification was effected by adding 1 equiv of triethylamine to a suspension in EtOAc, followed by filtration of the product.

Compounds **1a**,**b** (LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$, $PhCO_2^-$, BocAla) and **1a** (LG = 4-$NCC_6H_4CO_2^-$) were stable for at least 2 weeks in 50% D_2O in CD_3CN. This was also true for **1a** (LG = $CH_3CO_2^-$) in D_2O, although in 25 mM phosphate buffer in D_2O hydrolysis occurred with a half-life of 136 h at room temperature. The GABA and glutamate derivatives of **1a** also underwent hydrolytic decomposition, and their half-lives under buffered and unbuffered conditions were determined by ^{1}H NMR spectroscopy. For the GABA derivative, the half-life was 38 h in 25 mM phosphate buffer at pD 5.4 and 8 h at pD 7.1. For the glutamate derivative, the half-life was 70 h in pure D_2O and 26 h in 25 mM phosphate buffer at pD 5.4. None of the hydrolyses produced **2a** or **3a**.

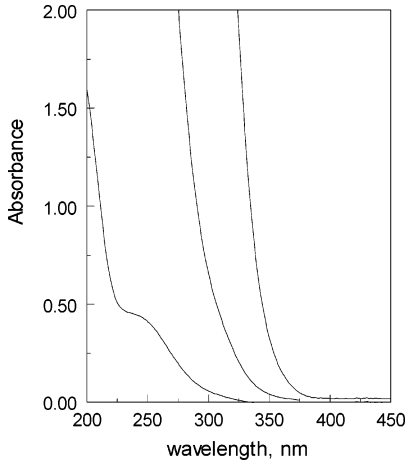


FIGURE 2. Absorption spectra of **1a** (LG = $CH_3CO_2^-$) at 0.070, 0.0070, and 0.00070 M in 50% aqueous acetonitrile.

Absorption Properties. In water and aqueous acetonitrile as solvents, α-keto amides **1a**,**b** show UV absorption maxima below 300 nm, and absorption tails out into the 300−350 nm region (Figure 2). For *N*,*N*-dialkyl α-keto amides, the n,π^* transition has been reported to occur at 315 nm in protic solvents.[10] At this wavelength, the corresponding extinction coefficient was ϵ 49 L mol^{-1} cm^{-1} for **1a** (LG = $CH_3CO_2^-$). The absorption properties of **1a**−**c** allowed routine photolyses of dilute 10^{-2} M solutions above 300 nm with Pyrex-filtered light or at 310 nm for quantum yield determinations. However, the α-keto amides absorbed only very weakly (ϵ < 10 L mol^{-1} cm^{-1}) at 355 nm, which necessitated high concentrations (>0.1 M) of compound to conduct laser flash photolysis experiments at this wavelength.

Photoproducts in Aqueous Media. Under aqueous conditions, the photolyses of 10^{-2}−10^{-1} M **1a**,**b** with Pyrex-filtered light (>300 nm) produced high yields of carboxylic acids along with one or more cleavage coproducts. In the case of the *N*,*N*-diethyl α-keto amides **1a**, the principal cleavage coproduct was the hemiacetal **2a**, which was obtained as a 3:2 mixture of diastereomers (eq 1), and α-methyleneoxazolidinone **3a** was only a minor product or was not observed (Table 1). In contrast, α-methyleneoxazolidinone **3b** was the sole cleavage coproduct obtained in photolyses of the *N*,*N*-diisopropyl α-keto amides **1b**, and hemiacetal **2b** was never observed (eq 2 and Table 2).

The above photolyses used 50% aqueous CH_3CN as the solvent. However, with **1a** (LG = $CH_3CO_2^-$, GABA, Glu), solubilities allowed a fully aqueous 25 mM phosphate buffer to be used as the medium. The product yields were typically determined by ^{1}H NMR spectroscopy for photolyses using the corresponding deuterated solvents (Tables 1 and 2). For **1a** (LG = $CH_3CO_2^-$), product yields were similar for photolyses conducted in 50% D_2O in CD_3CN (air or N_2 saturated), 100% D_2O, and 25 mM phosphate buffer at pD 7.

Photolyses of *N*-ethyl-*N*-phenyl amide **1c** (LG = $PhCH_2CO_2^-$) in 30% aqueous CH_3CN gave phenylacetic

(9) (a) Earle, M. J.; Abdur-Rashid, A.; Priestley, N. D. *J. Org. Chem.* **1996**, *61*, 5697−5700. (b) Gluchowski, C.; Bischoff, T. E.; Garst, M. E.; Kaplan, L. G.; Dietrich, S. W.; Aswad, A. S.; Gaffney, M. A.; Aoki, K. R.; Garcia, C.; Wheeler, L. A. *J. Med. Chem.* **1991**, *34*, 392−397. (c) Jefford, C. W.; Wang, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 634−635. (d) Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1980**, *44* (1), 199−202. (e) Andurkar, S. V.; Stables, J. P.; Kohn, H. *Bioorg. Med. Chem.* **1999**, 2381−2389. (f) Handa, S.; Hawes, J. E.; Pryce, R. J. *Synth. Commun.* **1995**, *25* (18), 2837−2845.

(10) Fischer, G.; Oehme, G.; Schellenberger, A. *Tetrahedron* **1971**, *27*, 5683−5695.

TABLE 1. Chemical Yields of Products from Steady-State Photolyses of α-Keto Amides 1a[a,b]

	yield, %			
LG^-	LG-H	**2a**	**3a**	**1a**
$CH_3CO_2^-$[c]	82	75	4.5	19
$PhCH_2CO_2^-$	86	66	10	12
$PhCO_2^-$[d]	93	88	<5	7
$PhCO_2^-$[c,e]	89	nd	nd	11
BocAla	81	78	0	18
$CH_3CONHCH_2CO_2^-$	75	77	0	24
4-$NCC_6H_4CO_2^-$	nd	85	0	13
GABA	75	83	0	20
Glu	70	54	15	22

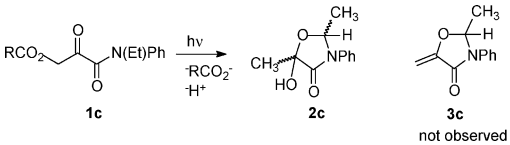
[a] Yields determined by ^{1}H NMR spectroscopy using DMSO, DMF, or glycine as a standard, unless noted otherwise. [b] Solvent was air-saturated 50% D_2O in CD_3CN, except for GABA and Glu, which used air-saturated D_2O containing 25 mM phosphate buffer as a solvent at pD 5 or 6, respectively. [c] Similar yields were obtained under nitrogen. [d] No standard was used, and run was performed under N_2. [e] Yields of $PhCO_2H$ and unreacted **1a** (LG = $PhCO_2^-$) determined by HPLC analysis.

TABLE 2. Chemical Yields of Products from Steady-State Photolyses of α-Keto Amides 1b[a,b]

	yield, %			
LG^-	LG-H	**2b**	**3b**	unreacted **1b**
$CH_3CO_2^-$	55	0	61	44
$PhCH_2CO_2^-$	86	0	82	17
$PhCO_2^-$	nd[b]	0	60	33
BocAla	88	0	86	10

[a] Yields determined by ^{1}H NMR spectroscopy using DMSO, DMF, or glycine as the standard. [b] Solvent was air-saturated 50% D_2O in CD_3CN; the product acid could not be determined due to overlapping of peaks with those of reactant **1b** (LG = $PhCO_2^-$).

acid and hemiacetal **2c** as a 11:7 mixture of diastereomers (eq 3). The α-methyleneoxazolidinone **3c** was not observed as a product. ^{1}H NMR analyses of photolyses conducted in the corresponding deuterated solvent showed 30% yield of **2c** and 40% of yield acid at 44% conversion. Photolyses of **1c** (LG = $PhCO_2^-$) were qualitatively similar to those of **1c** (LG = $PhCH_2CO_2^-$).



(3)

No evidence was found that the photolyses of **1a**−**c** (LG = $PhCH_2CO_2^-$) produced radical pairs. In these cases, the phenylacetyloxyl radicals produced by such radical cleavages would likely undergo rapid decarboxylation to give benzyl radicals.[11] Radical recombination products of benzyl radicals, including bibenzyl, were not observed.

To determine whether the observed products, hemiacetals **2** and α-methyleneoxazolidinones **3**, were stable under the aqueous acidic conditions used for the photolyses of **1a** and **1b**, control experiments were performed with each photoproduct in 50% D_2O in CD_3CN with added acetic acid (pD 2.8) in the dark. During a period of 14 days, **2a**, **3a**, and **3b** each remained unchanged according to ^{1}H NMR spectroscopic analyses with DMSO added as an NMR standard. These results indicated that, under the above conditions, **2a** and **3a** did not interconvert. In addition, **3b** did not give **2b**.

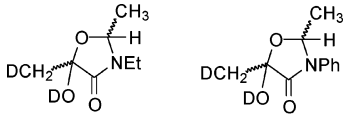
TABLE 3. Chemical Yields of Products from Steady-State Photolyses of α-Keto Amides 1a[a] in CD_3CN without Added Water

	yield, %			
LG^-	LG-H	**12a**	**3a**	**1a**
$CH_3CO_2^-$	0	59	<5	32
$PhCH_2CO_2^-$	9	68	8	25

[a] DMSO as the internal standard.

Deuterium Labeling. Information about the mechanisms for formation of hemiacetals **2a**,**c** and α-methyleneoxazolidinone **3a** under aqueous conditions in photolyses of *N*,*N*-diethyl- and *N*-ethyl-*N*-phenyl α-keto amides **1a**,**c** was provided by deuterium labeling studies. Such studies would also further address the possibility of interconversion of **2a** and **3a** and, in the case of *N*,*N*-diisopropyl α-keto amide **1b**, would provide the means to determine whether the unobserved hemiacetal **2b** could produce α-methyleneoxazolidinone **3b**.

When photolyses of **1a**,**c** (LG = $PhCO_2^-$, $PhCH_2CO_2^-$) were conducted in 50% D_2O in CD_3CN, diastereomeric hemiacetals **2a** and **2c** were found to be monodeuterated at the CH_3 group α to the carboxamide carbonyl group. The presence of deuterium was established by integration of the ^{1}H NMR signals at δ 1.54 and 1.47 and from the overlapping 1:1:1 patterns of peaks centered at δ 23.6 and 24.2 in the ^{13}C NMR spectrum.



2a-d_2 **2c**-d_2

The minor product of **1a**, α-methyleneoxazolidinone **3a**, was unlabeled at the α-methylene CH_2 group, whereas **3c** was not observed as a photoproduct of **1c**. As with **3a**, α-methyleneoxazolidinone **3b** contained no detectable deuterium at its α-methylene CH_2 group or elsewhere in the molecule when photolysis of **1b** was conducted in 50% D_2O in CD_3CN.

These deuterium labeling results show that the mechanistic pathway that leads to the labeling of **2a** does not produce **3a**, since such a pathway would also result in labeling of this latter product at the α-methylene position. The unlabeled α-methylene group of **3a** also indicates that **2a** and **3a** do not interconvert. For the same reason, **3b** is not formed from the unobserved hemiacetal **2b** as a precursor, which like **2a** and **2c**, would have been expected to be monodeuterated at its α-methyl group.

Photoproducts in Acetonitrile with No Added Water. Photolyses of **1a** (LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$) with Pyrex-filtered light in pure CH_3CN gave aminals **12a** (LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$) (eq 4, Table 3). The major conformational diastereomer of **12a** (LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$) showed a distinctive quartet in the δ 6.3 region of the ^{1}H NMR spectrum, and the minor diastereomer showed a downfield quartet in the δ 6.8 region. The aminals **12a** could be isolated in pure form by silica

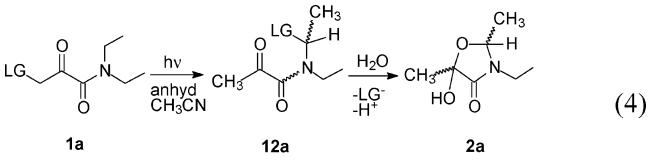
(11) (a) DeCosta, D. P.; Pincock, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 2180−2190. (b) Hilborn, J. W.; MacKnight, E.; Pincock, J. A.; Wedge, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 3337−3346. (c) Pincock, J. A. *Acc. Chem. Res.* **1997**, *30*, 43−49.

TABLE 4. Quantum Yields for Photocleavage and Time Constants for Bleaching of Bromocresol Green for α-Keto Amides 1a−c[a]

reactant	LG^-	Φ[b]	lifetime (μs)[c]
1a	$CH_3CO_2^-$	0.31[d]	137
	$PhCH_2CO_2^-$	0.36[e]	55.5
	BocAla	0.36[d]	29.7
	$4\text{-}NCC_6H_4CO_2^-$	0.38[e]	18.2
	$PhCO_2^-$	0.31[e]	nd[g]
	GABA	0.32[d]	nd
	Glu	0.38[d]	nd
	$CH_3CONHCH_2CO_2^-$	0.30[d]	nd
1b	$CH_3CO_2^-$	0.24[d,f]	132
	$PhCH_2CO_2^-$	0.25[e]	145
	$PhCO_2^-$	0.24[e]	124
	BocAla	0.31[f]	99
1c	$PhCH_2CO_2^-$	0.055[e]	nd
	$PhCO_2^-$	0.058[e]	nd

[a] Conducted in 50% aqueous CH_3CN, except for LG = GABA or Glu, which were determined in 25 mM phosphate buffer (pH = 5.4). [b] Average of two to four determinations. [c] Average error was less than 5% for **1a** and less than 10% for **1b**, except for LG = BocAla, which had 16% error. [d] Quantum yield for disappearance of reactant. [e] Quantum yield for appearance of carboxylic acid. [f] Quantum yield for appearance of **3b**. [g] Not determined.

gel chromatography. In contrast to **1a**, the *N*,*N*-diisopropyl amides, **1b** (LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$, $PhCO_2^-$, BocAla, BocGABA) did not give aminals when photolyzed in pure CH_3CN, and only the carboxylic acids and the α-methyleneoxazolidinones **3b** were observed as the products. As with photolyses under aqueous conditions, no recombination products derived from benzyl radicals were observed in the cases of **1a**,**b** (LG = $PhCH_2CO_2^-$).



(4)

LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$

When dissolved in aqueous CH_3CN, aminals **12a** hydrolyzed quantitatively to hemiacetals **2a**. ^1H NMR studies using 50% D_2O in CD_3CN as the solvent showed that product **2a** was deuterated only at the OH(D) group and nowhere else in the molecule. The disappearance of aminal **12a** (LG = $PhCH_2CO_2^-$) followed pseudo-first-order kinetics, and the half-life was ca. 3.1 h.

Quantum Yields. For the series of *N*,*N*-diethyl amides **1a**, quantum yields for reaction at 310 nm ranged from 0.24 to 0.38 in 50% aqueous CH_3CN and showed little variation for the series of carboxylate leaving groups (Table 4). In the case of **1a** (LG = $CH_3CO_2^-$) under fully aqueous conditions (H_2O or 25 mM phosphate buffer), quantum yields were 0.31−0.32, i.e., identical to those obtained in 50% aqueous CH_3CN (Table 4); furthermore, the quantum yields were essentially unchanged (Φ = 0.32) in D_2O containing 25 mM phosphate buffer (pD 5.1). Quantum yields were also similar (Φ = 0.32, 0.38) for 3 and 5 h respective photolysis times for disappearance of **1a** (LG = GABA, Glu) in 25 mM phosphate buffer at pH 5.4, after correction for the contributions due to hydrolysis of the reactants in the dark (vide supra).

Quantum yields for reaction of *N*,*N*-diisopropyl amide **1b** were 0.24−0.31 and similar to those for **1a**. For LG = $CH_3CO_2^-$, BocAla, the quantum yields for formation of **3b** were similar to the quantum yields for disappearance of the reactants. Compared to **1a**,**b**, the photochemistry of compound **1c** (LG = $PhCH_2CO_2^-$, $PhCO_2^-$) was substantially less efficient, Φ = ca. 0.05 for formation of the carboxylic acids.

Quantum yields for appearance of $PhCH_2CO_2H$ from **1a**−**c** (LG = $PhCH_2CO_2^-$) were similar to those for photocleavages that produce other carboxylic acids. No decreases in quantum yields were found due to decarboxylation[11] of phenylacetyloxyl radicals produced by a radical cleavage mechanism.

Photoinduced pH Changes. During photolyses in unbuffered 50% aqueous acetonitrile, the photolysates became acidic due to the presence of the photoreleased carboxylic acids. Starting at a pH of 6.1−6.6, the pH of the photolysates decreased by 2.6−3.3 units in the case of 0.04−0.05 M **1a**,**b** (LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$, BocAla). These pH jumps were sufficient to cause change in the color of the pH indicator bromocresol green (pK_a 4.90, 20 °C[12]). By monitoring the photolyses using absorption spectroscopy, the color change was found to correspond to decreased intensity (bleaching) of the 620 nm band of the anionic form of the indicator, and there was a corresponding increase in absorption at 420 nm.

Time-Resolved pH Jump Studies. To obtain information on the rates of release of protons and, indirectly, carboxylate anions from **1a**,**b**, the kinetics of bleaching of 15−20 μM bromocresol green pH indicator at 620 nm were studied by 355 nm nanosecond laser flash photolyses of 0.1−0.5 M **1a**,**b** in air-saturated 50% aqueous CH_3CN starting at a pH of 6−7 under unbuffered conditions. The samples had to be flowed in order to observe a signal. Each experiment represented a series of 10−30 shots from a Nd:YAG laser spaced at 30 or 60 s time intervals. The observed ΔOD versus time plots for each shot were summed together and then fit to a monoexponential function. This procedure furnished the time constants and hence, rate constants for the bleaching of the bromocresol green upon flash photolysis of **1a**,**b** (Table 4). Representative kinetic plots are shown for **1a**,**b** (LG = $PhCH_2CO_2^-$) in Figure 3A,B. Control experiments with α-keto amide **1a** (LG = H), which did not have a leaving group, showed no observable bleaching of the dye under the conditions used in the flash photolysis experiments.

For **1a**, the time constants for bleaching of bromocresol green strongly decreased with increasing leaving ability of the carboxylate groups (Table 4). The time constants τ followed the order $CH_3CO_2^-$ (pK_a 4.7) > $PhCH_2CO_2^-$ (pK_a 4.3) > BocAla (pK_a 4.02) > $4\text{-}CNC_6H_4CO_2^-$ (pK_a 3.6). A plot of log k versus $-pK_a$[13] gave a slope of 0.74 ± 0.07 σ (Figure 4). For **1b**, the time constants were insensitive to the basicity of the leaving group (Table 4).

Solvent isotope effects (H_2O/D_2O) for **1a** (LG = $PhCH_2CO_2^-$ and **1b** (LG = $PhCH_2CO_2^-$) were found to be opposite for the two compounds. An inverse solvent isotope effect of 0.74 ± 0.02 was observed for **1a** ($PhCH_2CO_2^-$), whereas a normal solvent isotope effect of 2.2 was observed for **1b** (LG = $PhCH_2CO_2^-$).

(12) *CRC Handbook of Chemistry and Physics*, 76th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 1995−1996; pp 8−17.

(13) (a) pK_a values: Rappoport, Z. In *CRC Handbook of Tables for Organic Compound Identification*, 3rd ed.; Weast, R. C., Ed.; CRC: Cleveland, 1967; pp 429−433. (b) BocAla, pK_a = 4.02, CA 15761-38-3.

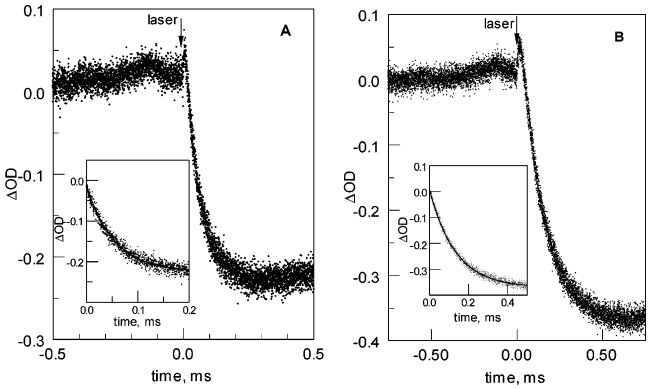


FIGURE 3. Kinetics of bleaching of bromocresol green at 620 nm upon laser flash photolysis of (A) **1a** (LG = $PhCH_2CO_2^-$) and (B) **1b** (LG = $PhCH_2CO_2^-$). Insets show the fit to a single-exponential decay function made after the transient spike due to cuvette luminescence in each case.

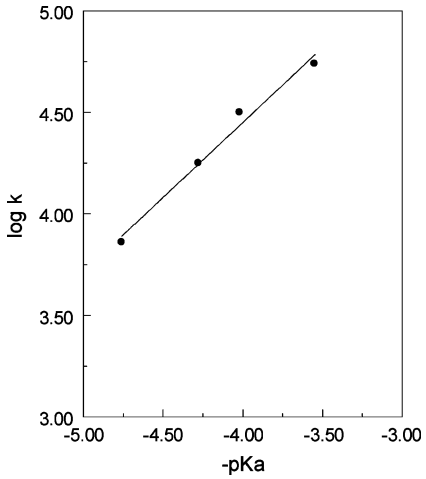


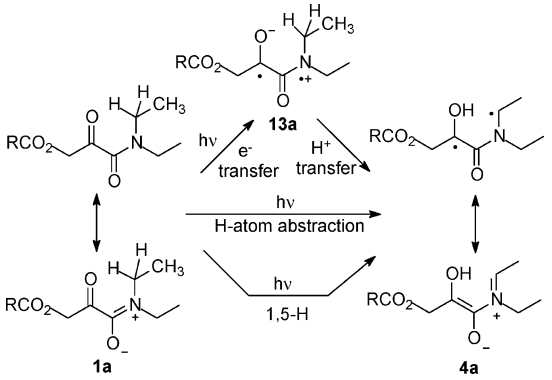
FIGURE 4. Log k vs $-pK_a$ plot for bleaching of bromocresol green by **1a** upon release of the carboxylic acids corresponding to LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$, BocAla, and 4-$NCC_6H_4CO_2^-$.

Discussion

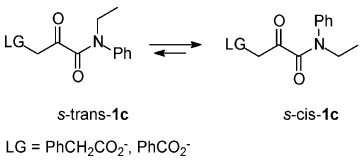
Photolyses of **1a**,**b** in aqueous solutions gave high yields of carboxylic acids for all of the carboxylate leaving groups tested (Figure 1). The cleavage coproducts **2a**, **2a** plus **3a**, or **3b** were formed in yields comparable to those of the carboxylic acids. Since these coproducts do not absorb light effectively above 300 nm, high photochemical conversions of **1a**,**b** were generally achievable. In most respects, the photochemistry of **1c** was similar to that of **1a** except that longer photolysis times were necessary to achieve significant conversions because of its low quantum yield for reaction.

The photocleavage reactions of **1a**,**b** are efficient (Φ > 0.2). The high quantum yields reflect, in part, efficient hydrogen transfer from an *N*-alkyl group to the keto oxygen upon generation of the excited state. The 5−7-fold lower efficiency of photocleavage of **1c** (Φ = ca. 0.05) may be attributable to the α-keto amide adopting mainly an *s*-cis conformation in the ground state (eq 5), which would be unreactive with respect to excited-state hydrogen transfer. ^{1}H NMR spectroscopic data suggest that **1c** exists as an 8:1 mixture of conformational isomers at

SCHEME 3



17 °C (see Results). Such a conformational dependence for excited-state hydrogen transfer has been previously shown for *N*-phenyl-*N*-ethyl α-keto amides that lack leaving groups.[4c,5] Nevertheless, an alternate rationale for the low efficiencies would invoke an electron-withdrawing effect of the *N*-phenyl group that retards or makes reversible the initial step of the reaction, which can be considered a net hydride transfer.



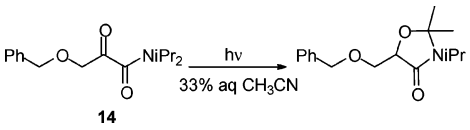
(5)

The mechanism for the initial, excited-state hydrogen transfer step of the reaction (Scheme 3) has not been definitively established, nor is the multiplicity of the excited-state known, although previous studies[5] have shown that the reactive excited state is nonemissive and nonquenchable via energy transfer, which would be consistent with the involvement of a short-lived singlet excited state. The hydrogen transfer could entail an excited-state hydrogen atom abstraction from an *N*-alkyl group, which would be consistent with a lowest energy n,π^* excited state.[10] Alternatively, a previous study[5] has proposed an initial electron transfer from amide nitrogen to the photoexcited keto group, followed by a proton transfer. A third mechanistic possibility would involve net hydride transfer from the amide alkyl group, which can be viewed as an excited-state 1,5-H shift, given the substantial double-bond character between amide carbonyl carbon and nitrogen in the ground state.

The photochemical hydrogen transfer would ultimately produce a ground-state intermediate that can be described as having zwitterionic character, as shown by structures **4a**−**c** (vide supra). Such zwitterionic intermediates are thought to be responsible for the release of the carboxylate leaving groups. Potentially competing with elimination are cyclizations of intermediates **4** to give oxazolidinones that retain the carboxylate leaving groups. Such cyclizations are well-precedented in the photochemistry of α-keto amides that have no leaving groups.[4,5,14] We have only observed oxazolidinone formation in the case of α-keto amide **14**,[2] which has a poor alkoxide leaving group (eq 6). For less basic leaving

(14) (a) Zehavi, U. *J. Org. Chem.* **1977**, *42*, 2821−2825. (b) Johansson, N. G.; Akermark, B.; Sjoberg, B. *Acta Chem. Scand. B* **1976**, *B30*, 383−390.

groups such as phenolates, 4-$ZC_6H_4O^-$ (Z = H, CF_3, or CN),[2] or carboxylates, elimination is invariably observed as the sole reaction under aqueous conditions.



(6)

A second potential cyclization reaction, which could compete with elimination, would be cyclization to form β-lactam products.[4,5,14b,15] β-Lactam formation, however, is thought to occur via a nonplanar, equilibrium conformer of **4** that has been described as a 1,4-diradical in electronic configuration.[5] We have never observed β-lactam photoproducts in photolyses of **1a**−**c** in aqueous media or in pure CH_3CN.

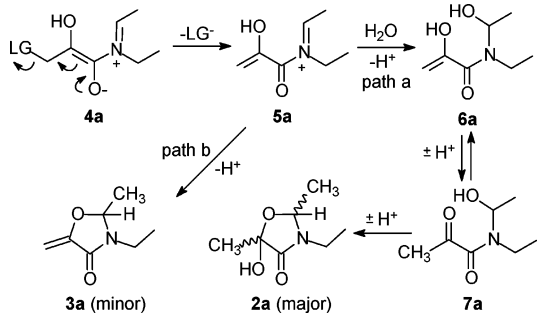
Initial studies to measure the rates of photochemical release of the carboxylic acids from **1a** utilized time-resolved difference FT-IR spectroscopy as a method[1] to directly monitor the 1560 cm^{-1} absorption of photoreleased carboxylate anions such as acetate and GABA in D_2O under buffered conditions. Use of a rapid scan technique showed that the photochemical formation of GABA occurred within 30 ms after the 355 nm laser pulse. Later experiments that used a step-scan technique with flowed samples of **1a** (LG = Glu) to obtain time constants on the microsecond time scale were unsuccessful, because of the weak absorption of the α-keto amide at 355 nm.

Permanent decreases in pH of aqueous photolysates were observed during steady-state photolyses of **1a**,**b**, which caused a change in the color of a pH indicator such as bromocresol green. The color change was due to a decrease in intensity of the 620 nm absorption of the bromocresol green, and there was a concomitant increase in absorption at 420 nm. These observations suggested that proton release rates could be obtained by a time-resolved pH jump method[8] using laser flash photolysis, which would determine the kinetics of the bleaching of the 620 nm absorption band of the bromocresol green.

For **1a** (LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$, BocAla, 4-$NCC_6H_4CO_2^-$), the time constants for bleaching of the 620 nm absorption of bromocresol green decrease with increasing leaving group ability of the carboxylate groups (Table 4). The leaving group effect (Figure 4) is substantial and would imply that the rate-determining step in the release of protons involves the elimination of carboxylate anions. According to Scheme 4, such carboxylate eliminations would occur in zwitterionic intermediates **4a**, prior to the proton release step that leads to hemiacetal **2** along path a. The observed inverse isotope effect of 0.74 would be consistent with the enolate group of **4a** being a stronger base in D_2O than H_2O, such that the elimination occurs more rapidly in the deuterated solvent,[16] whereas a normal solvent isotope effect would be expected if the subsequent proton release step along path a were rate determining.[17]

In the case of **1a**, the major pathway for proton release, path a, is thought to involve addition of water to an intermediate imminium ion **5a**, since pseudo-first-order rate constants ranging from 10^6 to 10^8 s^{-1} have been reported for a few examples in the literature.[18] Once proton release has occurred via path a, subsequent steps in the mechanism (Scheme 4) are needed to account for the formation of diastereomeric hemiacetals **2a**. These steps likely involve tautomerization[19] of **6a** followed by cyclization of **7a**. However, these acid-catalyzed reactions involve relatively stable compounds and are not considered to contribute to the rates of proton release and bleaching of the bromocresol green.

SCHEME 4



The formation of aminal products **12a** (eq 4, vide supra) in photolyses of **1a** (LG = $CH_3CO_2^-$, $PhCH_2CO_2^-$) in pure CH_3CN can be attributed to internal return of the ion pair comprised of the initially released carboxylate anion and imminium ion **5a**.[20] Such ion pair return would be expected in the absence of water. Under aqueous conditions, compounds **12a** hydrolyze to diastereomeric hemiacetals **2a** with release of the corresponding carboxylic acids. Since this hydrolytic release of acid occurs slowly, such aminals are unlikely to be intermediates in the release of protons from **1a** in the pH jump experiments performed under aqueous conditions.

Under aqueous conditions, products **2a** and **3a** are formed via two mechanistically distinct pathways (paths a and b, Scheme 4), according to deuterium labeling studies and control experiments. Compounds **2a** are not the source of the minor amounts of **3a** observed, because

(15) (a) Asahi, T.; Nakamura, M.; Kobayashi, J.; Toda, F.; Miyamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 3665−3669. (b) Natarajan, A.; Wang, K.; Ramamurthy, V.; Scheffer, J. R.; Patrick, B. *Org. Lett.* **2002**, *4*, 1443−1446.

(16) (a) An inverse isotope effect usually signifies the existence of a preequilibrium protonation step that is followed by a rate-determining step.[16b,c] We suspect that the isotope effect could be due to weaker solvation of the intermediate in D_2O than in H_2O, although the interpretation of the isotope effect is complicated by the fact that the pH rapidly changes in our unbuffered experiments. (b) Eldin, S.; Digits, J. A.; Huang, S.-T.; Jencks, W. P. *J. Am. Chem. Soc.* **1995**, *117*, 6631−6632. (c) Eldin, S.; Jencks, W. P. *J. Am. Chem. Soc.* **1995**, *117*, 4851−4857.

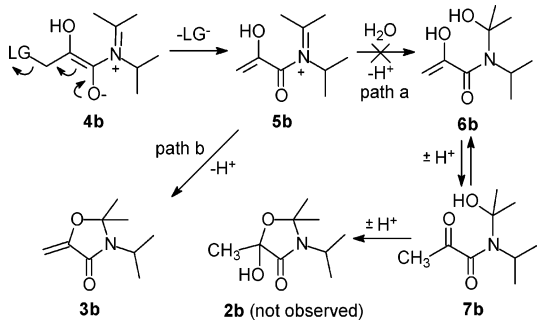
(17) Schowen, R. L. *Progress in Physical Organic Chemistry*; Wiley-Interscience: New York, 1972; Vol. 9, pp 275−332.

(18) (a) Keefe, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1983**, *105*, 265−279. (b) Keefe, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 2457−2459.

(19) Chiang, Y.; Kresge, A. J.; Santaballa, J. A.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 5506−5510.

(20) A referee has suggested a different view, namely, that 1,5-hydride shift to give **4a** in the *N*,*N*-diethyl compound **1a** depends on the solvent. Since the plus charge in zwitterions **4** would not be stabilized as much in **1a** as in the *N*,*N*-diisopropyl compound **1b**, the product difference for the two compounds in neat CH_3CN could be due to **1a** undergoing hydrogen atom abstraction to give a 1,4-diradical followed by loss of the leaving group as a radical. Cage recombination would then give **12a**. In the case of **1a** (LG = $PhCH_2CO_2^-$), the phenylacetyloxyl radical produced via radical cleavage would be expected to decarboxylate to benzyl radicals.[11] Although we observed no bibenzyl or other products of benzyl radicals, it is not guaranteed that the decarboxylation would effectively compete with rapid recombination of the caged radicals to give **12a**.

SCHEME 5



the latter product is found to contain no deuterium at the α-methylene group or elsewhere in the molecule, whereas the formation of **2a** results in incorporation of deuterium from D_2O at the methyl group α to the carboxamide carbonyl. The deuterium incorporation into **2a** would be indicative of a prior tautomerization step in the mechanism for its formation (Scheme 4). We also find that compound **3a** does not convert to **2a** under unbuffered aqueous photolysis conditions. At pD 2.8, compound **3a** remains unchanged over extended periods of time (14 days).

Although path a is the major pathway for product formation in the case of *N*,*N*-diethyl amides **1a**, only path b is apparently operative in the case of *N*,*N*-diisopropyl amides **1b**, since the sole photoproduct observed is **3b** (Scheme 5). Deuterium is not incorporated into **3b** from D_2O, and therefore, **3b** is not formed from **2b**, which would be an unobserved product of path a. Evidently, intramolecular trapping of the imminium ion group by the enolic hydroxyl of **5b** is more rapid than intermolecular addition of water to this intermediate.

In the case of **1b**, the time constants for bleaching of bromocresol green (Table 4) are much less sensitive to the nature of the leaving group as compared to those determined for **1a**. The small leaving group effect suggests that the intramolecular cyclization of **5b** (path b, Scheme 1) may be significantly rate determining. The greater importance of this step in determining the bleaching rates could be due to stabilization of both **4b** and **5b** relative to product **3b** by the extra methyl group at the imminium ion moiety. Rate-determining cyclization of **5b** would be consistent with the observed normal solvent isotope effect (H_2O/D_2O) on bleaching rates for **1b** (LG = $PhCH_2CO_2^-$) of 2.2.

Conclusion

α-Keto amides with various carboxylate leaving groups undergo photocleavage to form carboxylic acids and diastereomeric hemiacetals or α-methyleneoxazolidinones. The photoreaction is efficient, with quantum yields of 0.2−0.4 for *N*,*N*-diethyl and *N*,*N*-diisopropyl amides, whereas for *N*-ethyl-*N*-phenyl amides the photocleavage is inefficient, because the conformer required for hydrogen transfer from the *N*-ethyl group to the keto group in the excited state is disfavored.

The photoreleased carboxylic acids cause a decrease in pH of 2−3 units in aqueous solutions. The time constants for proton release were determined by monitoring the kinetics of bleaching of the 620 nm absorption of the pH indicator, bromocresol green, using nanosecond flash photolytic techniques. These time constants range from 18 to 137 μs for the *N*,*N*-diethyl amides and reflect the leaving group ability of the carboxylate groups. In contrast, for the *N*,*N*-diisopropyl amides the time constants are less sensitive to the nature of the leaving groups and range from 99 to 145 μs. The large leaving group effect and an inverse solvent isotope effect (H_2O/D_2O) on bleaching rates for the *N*,*N*-diethyl amides support a rate-limiting elimination of the carboxylate group in the postulated zwitterionic intermediate, whereas for the *N*,*N*-diisopropyl amides a subsequent step involving intramolecular cyclization and proton release is evidently significantly rate limiting.

The major cleavage coproducts, diastereomeric hemiacetals, which are observed for *N*,*N*-diethyl amides, are formed via intermolecular addition of water to an intermediate enolic imminium ion. On the other hand, intramolecular cyclization of an enolic hydroxyl group in an imminium ion intermediate produces exclusively the cleavage coproduct of the *N*,*N*-diisopropyl amides, an α-methyleneoxazolidinone. The postulated imminium ion produced initially upon carboxylate elimination can be trapped by the carboxylate anions when the photolyses of *N*,*N*-diethyl amides **1a** are conducted in CH_3CN without added water. Hydrolysis of these trapping products furnishes exclusively diastereomeric hemiacetals.

Experimental Section

HPLC analyses were performed on a 14.6 × 250 mm, 10 μm ODS-2 column eluting with 70% acetonitrile and 30% 25 mM phosphate ion buffer at 1.5 mL min^{-1}; UV (254 nm) detector response was calibrated using standard mixtures. Preparative chromatographic separations (MPLC) used a 2.5 × 28 cm column of 230−400 mesh silica gel eluting with 50% ethyl acetate in hexane at 15 mL min^{-1} with a pump, unless otherwise noted. The 25 mM phosphate ion buffer was prepared from 100 mM KH_2PO_4 and 150 mM NaCl in D_2O, adjusted to pD 7.4 with KOH, and then diluted 4-fold with deionized water.

Preparation of Acetic Acid, 3-(Diethylamino)-2-hydroxy-3-oxopropyl Ester 11a (LG = $CH_3CO_2^-$). A solution of 0.50 g (3.1 mmol) of *N*,*N*-diethyl-2,3-dihydroxypropanamide **10a** and 0.20 g (2.0 mmol) of acetic anhydride in 10 mL of CH_2Cl_2 was stirred at room temperature for 36 h. The reaction mixture was diluted by ethyl acetate, washed with 5% $NaHCO_3$ and saturated NaCl, and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by MPLC, eluting with 50% EtOAc in hexane to give 0.4 g (60% yield) of an oil. The spectral data were as follows: ^1H NMR ($CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H), 2.18 (S, 3H), 3.48 (dq, *J* = 14.2, 7.2 Hz, 1H), 3.29 (dq, *J* = 14.4, 7.5 Hz, 1H), 3.56 (dq, *J* = 14.4, 6.9 Hz, 1 H), 3.26 (dq, *J* = 14.2, 7.5 Hz, OH), 3.95 (ddd, *J* = 7.8, 4.5, 15.6 Hz, 2 H), 4.27 (dd, *J* = 3.0, 11.7, 1 H), 4.52 (dt, *J* = 3.0,7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 14.8, 21.5, 41.0, 41.5, 67.0, 67.3, 169.1, 170.4. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 52.89; H, 8.37; N, 6.79.

Preparation of Benzoic Acid, 3-(Diethylamino)-2-hydroxy-3-oxopropyl Ester 11a (LG = $PhCO_2^-$). To a solution of 4.0 g (25 mmol) of *N*,*N*-diethyl-2,3-dihydroxypropanamide **10a** in 20 mL of benzene was added, dropwise with stirring, 5.4 g (24 mmol) of neat benzoic anhydride at room temperature. The reaction was stirred for 36 h. The benzene was removed in vacuo, and ethyl acetate was added, followed by washing with 5% $NaHCO_3$ and saturated NaCl. After drying over Na_2SO_4, the solvent was removed in vacuo to give the crude product, which was purified by MPLC to give 2.2 g (35% yield) of **11a** (LG = $PhCO_2^-$) as a colorless oil. The spectral

data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.0 Hz, 3 H), 1.25 (t, J = 7.0 Hz, 3 H), 3.27 (dq, J = 13.5, 7.0 Hz 1 H), 3.31 (dq, J = 14.8, 7.0 Hz 1 H), 3.57 (dq, J = 14.8, 7.0 Hz 1 H), 3.61 (dq, J = 13.5, 7.0 Hz, 1 H), 4.12 (d, J = 6.3 Hz, OH), 4.25 (dd, J = 6.3,11.7 Hz, 1 H), 4.56 (dd, J = 3.0,11.7, 1 H), 4.68 (dt, J = 3.0, 7.0 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 2 H), 7.55 (t, J = 7.5 Hz, 1 H), 8.03 (d, J = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 14.9, 41.0, 41.6, 67.3, 128.1, 129.1, 129.4, 132.9, 165.9, 169.2. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.31; H, 7.13; N, 5.20.

Preparation of Phenylacetic Acid, 3-(Diethylamino)-2-hydroxy-3-oxopropyl Ester 11a (LG = $PhCH_2CO_2^-$). To a solution 5.4 g (34 mmol) of *N*,*N*-diethyl-2,3-dihydroxypropanamide **10a**, 1 mL of pyridine, and a catalytic amount DMAP in 40 mL of CH_2Cl_2 was added dropwise 5.0 g (32 mmol) of phenylacetyl chloride in 10 mL of CH_2Cl_2 over a 30 min period while stirring in an ice bath under N_2. After 24 h at room temperature, the reaction mixture was washed with water, 5% $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by MPLC to give 5.0 g (75% yield) of the product as an oil. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.0 Hz, 3 H), 1.20 (t, J = 7.0 Hz, 3 H), 3.78 (s, 2 H), 3.23 (dq, J = 13.5, 7.0 Hz 1 H), 3.25 (dq, J = 14.8, 7.0 Hz 1 H), 3.45 (dq, J = 13.5, 7.0 Hz 1 H), 3.55 (dq, J = 14.8, 7.0 Hz 1 H), 4.01 (dd, J = 7.2, 11.7 Hz, 1H), 4.35 (dd, J = 2.7, 11.4 Hz, 1H), 4.56 (d,t, J = 3.0, 7.5 Hz, 1H), 7.50 (m., 5 H); ^{13}C NMR ($CDCl_3$) δ 13.5, 14.9, 41.1, 41.6, 42.6, 67.3, 67.4, 127.0, 128.3, 129.0, 133.2, 169.1, 171.1. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.22; H, 7.69; N, 5.20.

Preparation of Acetic Acid, 3-(Diethylamino)-2,3-dioxopropyl Ester 1a (LG = $CH_3CO_2^-$). To a stirred solution of 1.5 g (7.1 mmol) of acetic acid 3-(diethylamino)-2-hydroxy-3-oxopropyl ester **11a** (LG = $CH_3CO_2^-$) in 70 mL of CH_2Cl_2 was added 3.9 g (18 mmol) of PCC at room temperature. After 24 h reaction, 100 mL of ether and 5 g of Florisil (60−100mesh) were added, followed by suction filtration. The filtrate was washed with 5% $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by MPLC to give 1.0 g (68% yield) of product. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.2 Hz, 3 H), 2.15 (s, 3 H), 3.35 (q, J = 7.2 Hz, 2 H), 3.88 (q, J = 7.2 Hz, 2 H), 5.0 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.3, 15.2, 21.1, 40.5, 42.7, 67.1, 163.2, 169.9, 192.1. Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.74; H, 7.53; N, 6.72.

Preparation of Benzoic Acid, 3-(Diethylamino)-2,3-dioxopropyl Ester 1a (LG = $PhCO_2^-$). The same method for synthesis of acetic acid 3-(diethylamino)-2,3-dioxopropyl ester **1a** (LG = $CH_3CO_2^-$) was used to prepare 2.3 g (70% yield) of α-keto amide **1a** (LG = $PhCO_2^-$) as a colorless oil from 3.3 g (12 mmol) of benzoic acid, 3-(diethylamino)-2-hydroxy-3-oxopropyl ester **11a** (LG = $PhCO_2^-$). The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 3 H), 1.23 (t, J = 7.2 Hz, 3 H), 3.42 (q, J = 7.2 Hz, 4 H), 5.28 (s, 2 H), 7.46 (m, 2 H), 7.59 (m, 1 H), 8.09 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.3, 14.2, 39.7, 42.0, 66.9, 128.1, 128.5, 129.6, 133.2, 163.5, 165.7, 192.6. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.02; H, 6.63; N, 5.36.

Preparation of Phenylacetic Acid, 3-(Diethylamino)-2,3-dioxopropyl Ester 1a (LG = $PhCH_2CO_2^-$). The same method for synthesis of acetic acid 3-(diethylamino)-2,3-dioxopropyl ester **1a** (LG = $CH_3CO_2^-$) was used to prepare 1.7 g (68% yield) of α-keto amide **1a** (LG = $PhCH_2CO_2^-$) as a colorless oil from 2.5 g (8.9 mmol) of phenylacetic acid, 3-(diethylamino)-2-hydroxy-3-oxopropyl ester **11a** (LG = $PhCH_2CO_2^-$). The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3 H), 1.21 (t, J = 7.2 Hz, 3 H), 3.35 (q, J = 7.2 Hz, 2H), 3.40 (q, J = 7.2 Hz, 2H), 5.07 (s, 2 H), 7.2−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.2, 15.1, 40.4, 41.0, 42.6, 67.3, 126.9, 128.2, 129.0, 132.8, 163.2, 170.5, 191.9. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.11; H, 7.06; N, 5.01.

Preparation of *N*-BOC-Alanine, 3-(Diethylamino)-2,3-dioxopropyl Ester 1a (LG = BocAla). To a solution of 2.2 g (14 mmol) of *N*,*N*-diethyl-2,3-dihydroxypropanamide **10a** and a catalytic amount of DMAP was added 2.0 g (10 mmol) of 2-(*tert*-butoxycarbonylamino)propionic acid (*N*-BocAla). After the carboxylic acid dissolved, 13 mL (1.0 M in CH_2Cl_2) of DCC was added under nitrogen over 15 min, and the reaction was stirred for 24 h at room temperature. The dicyclohexylurea was removed by suction filtration, and the filtrate was washed twice with water (10 mL), 5% $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to give 2.7 g of *N*-BOC-alanine 3-(diethylamino)-2-hydroxy-3-oxopropyl ester **11a** (LG = BocAla) as an oil. Without further purification, a solution of 2.7 g (8.3 mmol) of the oil in 30 mL of CH_2Cl_2 was stirred while adding 2.7 g (12 mmol) of PCC at room temperature. After 12 h of reaction, 10 mL of ether and 3 g of Florisil (60−100 mesh) were added, followed by suction filtration. The filtrate was washed with 5% $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by MPLC to give 1.8 g (69% yield) of crystalline product, which was crystallized from ethyl acetate in hexane to give material with mp 69−72 °C. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 6.9 Hz, 3 H), 1.23 (t, J = 6.9 Hz, 3 H), 1.45 (s, 9 H), 1.49 (d, J = 6.9 Hz, 1 H), 3.38-(q, J = 7.2 Hz, 2 H), 3.42 (q, J = 6.9 Hz, 2 H), 4.43 (qd, J = 6.9, 5.7 Hz, 1 H), 5.05 (d, J = 5.7 Hz, 1 H), 5.06 (d, J = 17.1 Hz, 1 H), 5.17 (d, J = 17.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.3, 19.3, 28.9, 40.6, 42.7, 49.5, 67.5, 80.2, 154.5, 163.0, 172.3, 191.4. Anal. Calcd for $C_{15}H_{26}N_2O_6$: C, 54.53; H, 7.93; N, 8.48. Found: C, 54.83; H, 7.88; N, 8.42.

Preparation of 4-Cyanobenzoic Acid, 3-(Diethylamino)-2,3-dioxopropyl Ester 1a (LG = 4-$CNC_6H_4CO_2^-$). To a solution of 1.6 g (9.9 mmol) of *N*,*N*-diethyl-2,3-dihydroxypropanamide **7a** and 1 mL of triethylamine in 20 mL of CH_2Cl_2 in an ice bath under nitrogen was added 1.3 g (8.0 mmol) of 4-cyanobenzoyl chloride over 15 min. The reaction was stirred for 24 h at room temperature and then washed twice with water (10 mL), 5% $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to give 1.4 g of 4-cyanobenzoic acid 3-(diethylamino)-2-hydroxy-3-oxopropyl ester **11a** (LG = 4-$CNC_6H_4CO_2^-$) as a colorless solid. Without further purification, a solution of 1.4 g (4.8 mmol) of the oil in 30 mL of CH_2Cl_2 was stirred while adding 1.5 g (7.2 mmol) of PCC at room temperature. After 12 h of reaction, 10 mL of ether and 3 g of Florisil (60−100 mesh) were added, followed by suction filtration. The filtrate was washed with 5% $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by MPLC to give 1.0 g (75% yield) of product as colorless crystals. Crystallization from ethyl acetate in hexane gave material with mp 90−91 °C. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3 H), 1.24 (t, J = 7.2 Hz, 3 H), 3.43(q, J = 7.2 Hz, 2 H), 3.44 (q, J = 7.2 Hz, 2 H), 5.35 (s, 2 H), 7.77 (d, J = 8.1 Hz, 2 H), 8.20 (d, J = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.8, 40.6, 42.6, 68.0, 117.1, 118.0, 130.5, 132.4, 132.9, 163.5, 164.6, 192.1. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.62; H, 5.65; N, 9.62.

Preparation of Acetylglycine, 3-(Diethylamino)-2,3-dioxopropyl Ester 1a (LG = $CH_3CONHCH_2CO_2^-$). To a solution of 1.8 g (11 mmol) of *N*,*N*-diethyl-2,3-dihydroxypropanamide **10a** and a catalytic amount of DMAP was added 1.0 g (8.5 mmol) *N*-acetylglycine. After the carboxylic acid dissolved, 10 mL (1.0 M in CH_2Cl_2) of DCC was added under nitrogen over 15 min, and the reaction was stirred for 24 h at room temperature. The dicyclohexylurea was removed by suction filtration; the filtrate was washed twice with water (10 mL), and the water was removed by distillation at reduced pressure to obtain crude ester **11a** (LG = $CH_3CONHCH_2CO_2^-$) as an oil. Without further purification, ester **11a** in 20 mL of CH_2Cl_2 was stirred while adding 2.4 g (12 mmol) of PCC at

room temperature. After 12 h of reaction, 10 mL of ether and 3 g of Florisil (60−100 mesh) were added, followed by suction filtration. The filtrate was concentrated in vacuo, and the residue was purified by MPLC to give 0.1 g (4% yield) of an oil. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H), 2.06 (s, 3H), 3.35 (q, J = 7.2 Hz, 2H), 3.40 (q, J = 7.2 Hz, 2H), 4.18 (br, 2H), 5.12 (s, 2H), 6.15 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.8, 13.2, 40.5, 41.3, 42.5, 67.6, 163.4, 169.7, 170.4, 192.1; MS (*m/z*) 230 (0.6), 158 (3.3), 141 (5.6), 100 (100), 72 (57.5). Anal. Calcd for $C_{11}H_{18}N_2O_5$: C, 51.16; H, 7.02; N, 10.85. Found: C, 51.30; H, 7.07; N, 10.57.

Preparation of *N*-BOC-GABA, 3-(Diethylamino)-2,3-dioxopropyl Ester 1a (LG = BOC-GABA). To a solution of 0.64 g (4.0 mmol) of *N*,*N*-diethyl-2,3-dihydroxypropanamide **10a** and a catalytic amount of DMAP in 20 mL of CH_2Cl_2 was added 0.71 g (3.5 mmol) of 4-(*tert*-butoxycarbonylamino)butyric acid (*N*-BOC-GABA). After the carboxylic acid dissolved, a solution of 0.78 g (3.5 mmol) of DCC in 10 mL of CH_2Cl_2 was added under nitrogen over 15 min. The reaction was stirred for 24 h at room temperature. The mixture was washed with water, 5% $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to give 0.50 g (46% yield) of *N*-BOC-GABA, 3-(diethylamino)-2-hydroxy-3-oxopropyl ester (**11a**, LG = BocGABA), as an oil. The hydroxyamide was oxidized to α-keto amide **1a** (LG = BocGABA) in 80% yield by the same procedure used to prepare the acetic acid ester derivative **1a** (LG = $CH_3CO_2^-$). Crystallization from ether in hexane gave the product as white crystals, mp 68−70 °C. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3 H), 1.46 (s, 9 H), 1.88 (qui, J = 7.2 Hz, 2 H), 2.51 (t, J = 7.2 Hz, 2 H), 3.31 (br q, J = 7.2 Hz, 2 H), 3.39 (q, J = 7.2 Hz, 2 H), 3.43 (q, J = 7.2 Hz, 2 H), 4.69 (br, 1 H, NH), 5.07 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ? 13.4, 15.3, 25.9, 29.1, 31.6, 40.2, 40.5, 42.7, 67.1, 79.2, 156.5, 163.2, 172.1, 192.1. Anal. Calcd for $C_{16}H_{28}N_2O_6$: C, 55.79; H, 8.19; N, 8.13. Found: C, 55.44; H, 7.93; N, 7.78.

Preparation of *N*-BOC-Glutamate, 3-(Diethylamino)-2,3-dioxopropyl Ester 1a (LG = BocGlu). The same method used to prepare *N*,*N*-diethyl α-keto amide **1a** (LG = BocGABA) was used to prepare 1.3 g (60% yield) of α-keto amide **1a** (LG = BocGlu) as an oil, starting from 2.2 g (5.0 mmol) of *N*-BOC-glutamate, 3-(diethylamino)-2-hydroxy-3-oxopropyl ester **11a** (LG = BocGlu). The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.38 (s, 9 H), 1.41 (s, 9 H), 1.90 (m, 1 H), 2.12 (m, 1 H), 2.46 (t, J = 7.2 Hz, 1 H), 2.50 (t, J = 7.2 Hz, 1 H), 3.32 (q, J = 7.2 Hz, 2 H), 3.36 (q, J = 7.2 Hz, 2 H), 4.16 (m, 2 H), 4.98 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.2, 15.4, 28.8, 29.2, 29.3, 30.7, 40.8, 40, 42.9, 53.9, 67.4, 80.1, 82.6, 155.1, 163.5, 170.8, 171.9, 192.2. Anal. Calcd for $C_{21}H_{36}N_2O_8$: C, 56.74; H, 8.16; N, 6.30. Found: C, 56.29; H, 7.93; N, 6.23.

General Procedure for Deprotection of 1a (LG = BocGABA, BocGlu). To an ice-cooled, stirred solution of 0.50 mmol of **1a** (LG = BocGABA, BocGlu) in 10 mL of CH_2Cl_2 under argon was added dropwise a solution of 1.5 mmol of TFA in 5 mL of CH_2Cl_2. After 30 min, the reaction mixture was allowed to warm to room temperature and was stirred for 24 h, followed by concentration in vacuo. The crude trifluoroacetate salt was dissolved in deionized water and chromatographed on Sephadex LH-20, eluting with deionized water. For the GABA derivative **1a** (LG = GABA), only a single chromatographic peak was detected by absorption at 254 nm. For the glutamate derivative **1a** (LG = Glu), only the early portion of the peak was collected, omitting a later eluting shoulder. The trifluoroacetate salts **1a** (LG = GABA, Glu) were obtained after lyophilization as hygroscopic, colorless powders in 70 and 68% yield, respectively. To reduce the CF_3CO_2H content of **1a** (LG = Glu), 1 equiv of triethylamine was added to a suspension of the salt in EtOAc, followed by filtration of the solid product; triethylammonium trifluoroacetate was present in the filtrate, and negligible **1a** (LG = Glu) was found in the EtOAc. The spectral data below were obtained in 25 mM pD 7.4 phosphate buffer prepared in D_2O.

Trifluoroacetate Salt of α-Keto Amide 1a (LG = GABA). The spectral data were as follows: ^{1}H NMR (D_2O) δ 1.16 (t, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.2 Hz, 3 H), 2.25 (ddt, J = 21.0, 7.2, 7.2 Hz, 1 H), 2.75 (td, J = 7.2, 2.9 Hz, 2 H), 3.38 (q, J = 7.2 Hz, 2 H), 3.42 (q, J = 7.2 Hz, 2 H), 3.98 (t, J = 7.2 Hz, 1 H), 5.18 (s, 2 H); ^{13}C NMR (D_2O) δ 15.0, 16.7, 28.4, 32.5, 43.4, 46.0, 55.7, 70.1, 116.4 (q, J = 383 Hz), 162.38 (q, J = 46.5 Hz), 167.0, 174.3, 175.3, 197.5.

α-Keto Amide 1a (LG = Glu). Colorless solid, mp 103−105 °C. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3 H), (t, J = 7.2 Hz, 3 H), 1.97 (qui, J = 7.5 Hz, 2 H), 2.62 (t, J = 7.2 Hz, 2 H), 3.03 (br t, J = 7.5 Hz, 2 H), 3.35 (q, J = 7.2 Hz, 2 H), 3.39 (q, J = 7.2 Hz, 2 H), 5.14 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.6, 14.3, 22.9, 31.0, 39.3, 40.9, 43.5, 67.6, 116.4 (q, J = 383 Hz), 162.4 (q, J = 46.5 Hz), 164.5, 173.2, 195.0. Anal. Calcd for $C_{14}H_{21}N_2O_8 \cdot 0.26CF_3CO_2H$: C, 47.29; H, 6.42; N, 8.81. Found: C, 47.27; H, 6.31; N, 8.84.

Preparation of Acetic Acid, 3-(Diisopropylamino)-2,3-dioxopropyl Ester 1b (LG = $CH_3CO_2^-$). The same method for the synthesis of benzoic acid 3-(diethylamino)-2-hydroxy-3oxopropyl ester **11a** (LG = $PhCO_2^-$) was used to prepare 0.4 g (60% yield) of acetic acid, 3-(diisopropylamino)-2-hydroxy-3-oxopropyl ester **11b** (LG = $CH_3CO_2^-$), as a colorless oil from 0.53 g (2.8 mmol) of *N*,*N*-diisopropyl-2,3-dihydroxypropanamide **10b**. Oxidation of 0.81 g (3.5 mmol) of acetic acid, 3-(diisopropylamino)-2-hydroxy-3-oxopropyl ester **11b** (LG = $CH_3CO_2^-$) by PCC gave 0.6 g (70% yield) of α-keto amide **1b** (LG = $CH_3CO_2^-$) after MPLC purification. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6.9 Hz, 6 H), 1.44 (d, J = 6.9 Hz, 6 H), 2.17 (s, 3 H), 3.52 (sept, J = 6.9 Hz, 1 H), 3.94 (sept, J = 6.9 Hz, 1 H), 4.93 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.1, 21.4, 46.7, 50.2, 66.7, 164.4, 169.9, 192.6. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.65; H, 8.41; N, 6.06.

Preparation of Benzoic Acid, 3-(Diisopropylamino)-2,3-dioxopropyl Ester 1b (LG = $PhCO_2^-$). The same method for synthesis of acetic acid 3-(diethylamino)-2,3-dioxopropyl ester **1a** (LG = $CH_3CO_2^-$) was used to prepare 1.3 g (67% yield) of α-keto amide **1b** (LG = $PhCO_2^-$) as a colorless oil from 2.0 g (6.6 mmol) of benzoic acid, 3-(diisopropylamino)-2-hydroxy-3-oxopropyl ester **11b** (LG = $PhCO_2^-$). The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 6 H), 1.43 (d, J = 6.9 Hz, 6 H), 3.53 (sept, J = 6.9 Hz, 1 H), 4.03 (sept, J = 6.9 Hz, 1 H), 5.20 (S, 2 H), 8.10 (d, J = 7.2 Hz, 2 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.60 (t, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.4, 46.7, 50.3, 67.1, 128.2, 128.6, 129.6, 133.3, 164.4, 165.6, 192.7. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.22; N, 4.81. Found: C, 66.23; H, 7.42; N, 4.82.

Preparation of Phenylacetic Acid, 3-(Diisopropylamino)-2,3-dioxopropyl Ester 1b (LG = $PhCH_2CO_2^-$). To a solution of 1.1 g (5.8 mmol) of *N*,*N*-diisopropyl-2,3-dihydroxypropanamide **10b**, 5 mL (1.0 M in CH_2Cl_2) of DCC, and a catalytic amount DMAP in 10 mL of CH_2Cl_2 was added dropwise with stirring 0.53 g (3.9 mmol) of phenylacetic acid at room temperature. After 12 h of reaction, the dicyclohexylurea was removed by filtration, and the filtrate was washed twice with water and saturated NaCl and then dried over Na_2SO_4. The solvent was removed in vacuo to give the crude product, which was purified by MPLC to give 0.96 g (80% yield) of the ester as a colorless oil. To a solution of 0.96 g (3.1 mmol) of the ester in 10 mL of CH_2Cl_2 was added 1.0 g (4.5 mmol) of PCC at room temperature. After 12 h of reaction, 10 mL of ether and 3 g of Florisil were added followed by suction filtration. The filtrate was washed by saturated NaCl and then dried over Na_2SO_4. The solvent was removed in vacuo to give the crude product, which was purified by MPLC to give the ester as a colorless oil. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 6.6 Hz, 6 H), 1.40 (d, J = 6.9 Hz, 6 H), 3.49 (sept, J = 6.6 Hz, 1 H), 3.74 (s, 2H), 3.90 (sept, J = 6.6 Hz, 1 H), 4.96 (s, 2 H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ

20.3, 20.5, 40.8, 46.4, 50.0, 67.0, 127.3, 128.8, 129.5, 133.3, 195.0, 171.3, 193.1. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.11; H, 7.74; N, 4.60.

Preparation of *N*-BOC-Alanine, 3-(Diisopropylamino)-2,3-dioxopropyl Ester 1b (LG = BocAla). To a solution of 3.3 g (18 mmol) of *N*,*N*-diisopropyl-2,3-dihydroxypropanamide and a catalytic amount of DMAP was added 2.6 g (14 mmol) of 2-(*tert*-butoxycarbonylamino)propionic acid (*N*-BOC-ala). After the carboxylic acid dissolved, 14 mL (1.0 M in CH_2Cl_2) of DCC was added under nitrogen over 20 min, and the reaction was stirred for 24 h at room temperature. The dicyclohexylurea was removed by suction filtration, and the filtrate was washed twice with water (10 mL), 5% $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to give 3.4 g of crude *N*-BOC-alanine 3-(diethylamino)-2-hydroxy-3-oxopropyl ester **11b** (LG = BocAla) as a colorless oil. Without further purification, a solution of 3.4 g (9.4 mmol) of the oil in 30 mL of CH_2Cl_2 was stirred while adding 2.9 g (14 mmol) of PCC at room temperature. After 10 h of reaction, 10 mL of ether and 3 g of Florisil (60−100 mesh) were added, followed by suction filtration. The filtrate was washed with 5% $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by MPLC to give 2.8 g (59% yield) of crystalline product, which was crystallized from ethyl acetate in hexane to give material with mp 88−89 °C. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H), 1.43 (d, J = 6.6 Hz, 3H), 1.44 (d, J = 6.6 Hz, 3H), 1.44 (S, (H), 1.48 (d, J = 6.6 Hz, 3H), 3.53 (sept, J = 6.6 Hz, 1H), 3.94 (sept, J = 6.6 Hz, 1H), 4.43(m, 1H), 4.97 (d, J = 17.1 Hz, 3 H), 5.08 (d, J = 17.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 19.0, 20.4, 21.0, 28.6, 46.6, 49.3, 50.0, 67.0, 80.2, 155.1, 164.8, 173.1, 192.7; MS (*m*/*z*) 358 (M^+, 0), 274 (4), 170 (8), 128 (82), 100 (13), 86 (100), 57 (27). Anal. Calcd for $C_{17}H_{30}N_2O_6$: C, 56.97; H, 8.44; N, 7.82. Found: C, 57.07; H, 8.41; N, 7.78.

Preparation of Benzoic Acid, *N*-Ethyl-*N*-phenyl-2,3-dioxopropanamide 1c (LG = $PhCO_2^-$). To a solution of 3.18 g (15.2 mmol) of *N*-ethyl-*N*-phenyl-2,3-dihydroxypropanamide **10c** in 50 mL of CH_2Cl_2 were added a catalytic amount DMAP and 15 mL of (15 mmol) of 1 M DCC in CH_2Cl_2. While stirring under N_2, a solution of 1.8 g (15 mmol) of benzoic acid in 20 mL of CH_2Cl_2 was added, followed by 12 h of reaction. The dicyclohexylurea was filtered, and the filtrate was concentrated to obtain crude product. Without further purification, the crude product was dissolved in 40 mL of CH_2Cl_2, and 4.6 g (22 mmol) of PCC was added. The reaction was stirred for 6 h, and then 100 mL of ether and 5 g of Florisil (60−100 mesh) were added, followed by suction filtration. The filtrate was washed with 5% $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by MPLC to give 2.8 g (60% yield), based on starting amide **10c**. Crystallization from EtOAc in hexane gave colorless crystals, mp 86−89 °C. The spectral data for the α-keto amide product were as follows: ^{1} H NMR ($CDCl_3$) δ 1.19 (t, J = 6.9 Hz, 3H), 3.87 (q, J = 6.9 Hz, 2H), 5.15 (S, 2H), 7.43 (m, 2H), 7.48 (m, 5H) 7.60 (m, 1H), 8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.9, 44.6, 67.2, 126.69 (127.63), 128.6, 129.6, 129.1, 130.0, 133.6, 139.5, 163.9, 165.4, 192.6; MS (*m*/*z*) 311 (M^+, 1), 163 (60), 148 (84), 120 (100), 105 (78), 77 (68). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.47; H, 5.62; N, 4.68.

Preparation of Phenylacetic Acid, *N*-Ethyl-*N*-phenyl-2,3-dioxopropanamide 1c (LG = $PhCH_2CO_2^-$). To a solution of 0.64 g (3.0 mmol) of *N*-ethyl-*N*-phenyl-2,3-dihydroxypropanamide **10c** in 20 mL of CH_2Cl_2 were added a catalytic amount of DMAP and 2.5 mL (2.5 mmol) of 1 M DCC in CH_2Cl_2. While stirring, a solution of 0.34 g (2.5 mmol) of phenylacetic acid in 5 mL of CH_2Cl_2 was added under nitrogen. After 12 h of reaction, the dicyclohexylurea was removed by filtration, and the filtrate was concentrated to obtain the crude product. Without further purification, the crude product was dissolved in 20 mL of CH_2Cl_2, and 0.74 g (3.4 mmol) of PCC was added. The reaction was stirred for 6 h, and then 100 mL of ether and 2 g of Florisil (60−100 mesh) were added, followed by suction filtration. The filtrate was washed with 5% $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by MPLC to give 0.75 g (75% yield). The spectral data for the α-keto amide product were as follows (signals in parentheses due to a second conformer): ^{1} H NMR ($CDCl_3$) δ 1.08 (t, J = 6.9 Hz, 3H), 3.62 (s, 2H), 3.75 (q, J = 6.9 Hz, 2H), 4.90 (s, 2H) (5.08 (s, 2H)), 7.02 (m, 2H), 7.30 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 12.9, 41.0, 44.5, 67.1, 127.6 (127.4), 128.7 (128.6), 129.7 (129.4), 133.4, 139.4, 163.8, 170.3, 192.5; MS (*m*/*z*) 311 (2), 163 (71), 148 (91), 120 (100), 105 (72), 77 (59), 51 (12). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.90; H, 6.01; N, 4.41.

Preparative Photolysis of α-Keto Amide 1a (LG = $PhCO_2^-$) in Aqueous CH_3CN. A solution of 1.0 g (3.8 mmol) of **1a** (LG = $PhCO_2^-$) in 25 mL of 50% aqueous acetonitrile in a quartz tube was flushed with N_2 and irradiated through a Pyrex filter with a water-jacketed Hanovia 450 W medium-pressure mercury lamp for 3 h. The sample was at room temperature during photolysis. NMR analysis of an aliquot showed 94% conversion. The photolysate was extracted three times with ethyl acetate. To further facilitate removal of reactant, benzoic acid, and **3a**, ethyl acetate was added to the aqueous phase, and the mixture was frozen in dry ice overnight. After thawing, the organic phase was removed, and the addition of ethyl acetate and freezing was repeated two more times. The final aqueous solution, after separation of ethyl acetate, was lyophilized to give the diastereomeric hemiacetals **2a**. A small amount of oxazolidinone **3a** was isolated from the concentrated organic extracts by MPLC, eluting with 50% ethyl acetate in hexane.

The spectral data for the major diastereomer of hemiacetals **2a** were as follows: ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3 H), 1.35 (d, J = 5.5 Hz, 3 H), 1.52 (s, 3 H), 3.11 (dq, J = 14.0, 7.2 Hz, 1 H), 3.45 (dq, J = 14.0, 7.2 Hz, 1 H), 5.30 (q, J = 5.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.7, 20.1, 23.5, 34.6, 83.6, 98.4, 169.4. The spectral data for the minor diastereomer of hemiacetals **2a** were as follows: ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3 H), 1.44 (d, J = 5.5 Hz, 3 H), 1.47 (s, 3 H), 3.09 (dq, J = 14.0, 7.2 Hz, 1 H), 3.51 (dq, J = 14.0, 7.2 Hz, 1 H), 5.10 (q, J = 5.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.6, 21.3, 22.8, 34.8, 83.9, 99.0, 169.0. Anal. Calcd for diastereomeric mixture of hemiacetals $C_7H_{13}NO_3 \cdot 0.26\ H_2O$: C, 50.76; H, 8.35; N, 8.46. Found: C, 50.76; H, 8.28; N, 8.66.

The spectral data for oxazolidinone **3a** were as follows: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.2 Hz, 3 H), 1.49 (d, J = 5.4 Hz, 3 H), 3.21 (dq, J = 14.0, 7.2 Hz, 1 H), 3.69 (dq, J = 14.0, 7.2 Hz, 1 H), 4.56 (d, J = 2.4 Hz, 1 H), 4.90 (d, J = 2.4 Hz, 1 H), 5.44 (q, J = 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.2, 21.0, 35.2, 86.2, 86.9, 150.8, 160.7. The compound was too volatile for successful elemental analysis.

Preparative Photolysis of α-Keto Amide 1b (LG = $PhCO_2^-$) in Aqueous CH_3CN. A solution of 0.50 g (1.7 mmol) of **1b** (LG = $PhCO_2^-$) in 25 mL of 50% aqueous acetonitrile in a quartz tube was flushed with N_2 and irradiated through a Pyrex filter with a water-jacketed Hanovia 450 W medium-pressure mercury lamp for 3 h. The sample was at room temperature during photolysis. After extraction with ethyl acetate three times, the combined extracts were washed with 5% $NaHCO_3$ and saturated NaCl and dried over $MgSO_4$, and the solvent was removed in vacuo to give an oil. The oil was chromatographed (MPLC), eluting with 25% EtOAc in hexane, to give starting material **1b** (LG = $PhCO_2^-$), which eluted first, and a colorless crystalline product **3b**, mp 47−48 °C. The spectral data were as follows: ^{1}H NMR ($CDCl_3$) δ 1.50 (d, J = 6.6 Hz, 6 H), 1.53 (s, 6 H), 3.47 (sept, J = 6.6 Hz, 1H), 4.46 (d, J = 2.1 Hz, 1 H), 4.83 (d, J = 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 27.1, 46.5, 85.0, 95.3, 150.2, 159.7. Anal. Calcd for oxazolidinone **3b** $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.60; H, 9.08; N, 8.05.

Preparative of Photolysis of Acetic Acid and Phenylacetic Acid Derivatives of α-Keto Amide 1a (LG =

$CH_3CO_2^-$, $PhCH_2CO_2^-$) in CD_3CN. A solution of 0.30 g (1.1 mmol) of **1a** (LG = $PhCH_2CO_2^-$) in CD_3CN in an NMR tube was purged with N_2 and then irradiated through a Pyrex filter with a water-jacketed Hanovia 450 W medium-pressure mercury lamp for 75 min. The temperature was 26 °C during photolysis. The NMR sample was directly applied to the MPLC column and eluted with 50% ethyl acetate in hexane to give unreacted **1a** (LG = $PhCH_2CO_2^-$), which eluted first, followed by phenylacetate ester **12a** (LG = $PhCH_2CO_2^-$) and a minor amount of oxazolidinone **3a**. The ^1H NMR spectrum **12a** (LG = $PhCH_2CO_2^-$) showed ca. 10% of a minor C−N conformer, which exhibited a $>CHO_2CCH_2Ph$ methine quartet at δ 6.8. The spectral data for **12a** (LG = $PhCH_2CO_2^-$) were as follows: ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3 H), 1.54 (d, J = 6.0 Hz, 3 H), 2.48 (s, 3 H), 3.19 (dq, J = 14.0, 7.2 Hz, 1 H), 3.34 (dq, J = 14.0, 7.2 Hz, 1 H), 3.58 (s, 2 H), 6.63 (q, J = 6.0 Hz, 1 H), 7.1−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.8, 19.2, 27.5, 27.5, 35.7, 41.9, 78.8, 127.1, 128.4, 128.8, 132.7, 166.9, 170.3, 197.4. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.97; H, 6.92; N, 5.16.

In the case of **1a** (LG = $CH_3CO_2^-$), the same mmol amount of starting material was irradiated, and the mixture was separated by MPLC to give starting material **1a** (LG = $CH_3CO_2^-$) as the first eluting peak followed by **12a** (LG = $CH_3CO_2^-$), which was obtained as an oil. The spectral data for **12a** (LG = $CH_3CO_2^-$) were as follows: ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3 H), 1.55 (d, J = 6.0 Hz, 3 H), 2.04 (s, 3 H), 2.51(s, 3 H), 3.32 (dq, J = 14.0, 7.2 Hz, 1 H), 3.48 (dq, J = 14.0, 7.2 Hz, 1 H), 6.32 (q, J = 6.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.9, 19.2, 21.7, 27.5, 35.8, 78.4, 167.0, 169.9, 197.4. Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.91; H, 7.38; N, 7.23.

Preparative Photolysis of α-Keto Amide 1c (LG = $PhCH_2CO_2^-$) in Aqueous CH_3CN. A solution of **1c** (LG = $PhCH_2CO_2^-$) in 25 mL of 30% aqueous CH_3CN was photolyzed for 48 h. The sample was at room temperature during photolysis. The light brown photolysate was extracted by EtOAc and concentrated in vacuo. The crude colorless solid was chromatographed (MPLC), eluting with 25% EtOAc in hexane to obtain a product, which was crystallized from ether in EtOAc to obtain diasteromeric hemiacetals **2c**, mp 122−124 °C. The spectral data for the major diastereomer were as follows: ^1H NMR ($CDCl_3$) δ 1.24 (d, J = 5.4 Hz, 3H), 1.55 (s, 3H), 4.2 (br, 1H), 5.71 (q, J = 5.4 Hz, 1H), 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.7, 24.3, 85.6, 99.1, 123.9, 127.0, 129.4, 134.9, 168.9. The spectral data for the minor diastereomer were as follows: ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 5.4 Hz, 3H), 1.49 (s, 3H), 4.2 (br, 1H), 5.58 (q, J = 5.4 Hz, 1H), 7.11 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.0, 23.7, 86.3, 99.8, 123.2, 127.0, 129.5, 134.9, 168.5. Anal. Calcd for the mixture of diastereomers $C_{11}H_{13}NO_3$: C, 63.74; H, 6.32; N, 6.76. Found: C, 63.57; H, 6.23; N, 6.80.

General Procedure for Product Quantum Yield Determinations. The semimicrooptical bench for quantum yield determinations is similar to the apparatus described by Zimmerman.[21] Light from a 200 W high-pressure mercury lamp was passed through an Oriel monochromator, which was set to 310 nm wavelength, and collimated through a lens. A fraction of the light was diverted 90° by a beam splitter to a 10 × 3.6 cm side quartz cylindrical cell containing actinometer. The photolysate was contained in a 10 × 1.8 cm quartz cylindrical cell of 25 mL volume. Behind the photolysate was mounted a quartz cylindrical cell containing 25 mL of actinometer. Light output was monitored by ferrioxalate actinometry[22] using the splitting ratio technique. The samples were not purged with nitrogen.

General Procedure for Photolyses of Carboxylic Acid Derivatives of α-Keto Amides 1a,b in D_2O Solutions and Controls on Hydrolytic Stability of 1a,b in the Dark. Samples of 0.07−0.16 mmol of α-keto amides **1a**,**b** in 1 mL of D_2O, or in 0.25 mM phosphate ion buffer in D_2O (pD 5.4), or 50% D_2O in CD_3CN were contained in NMR tubes. The temperature throughout the photolyses was 26 °C. Samples were mounted beside a water-jacketed 450 W medium-pressure mercury lamp equipped with a Pyrex filter. Samples were also kept in the dark to determine stability at room temperature. The results in Tables 1−3 generally required 0.5−1 h photolysis times. Yields were determined by ^1H NMR spectroscopy using DMSO as the standard, except for **1a** (LG = Glu), which used DMF, and **1a** (LG = GABA), which used glycine.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (M.G.S.), and to the National Science Foundation for a Career Award (R.R.) for support of this research.

Supporting Information Available: ΔOD vs time plots for bleaching of bromocresol green by **1a** (LG = $CH_3CO_2^-$, BocAla, 4-$NCC_6H_4CO_2^-$) and by **1b** ($CH_3CO_2^-$, $PhCO_2^-$, BocAla); ^1H and ^{13}C NMR spectral data for **3a** and **10c**; and procedures for preparation of **9a**,**b**, **10a**−**c**, and **11b** (LG = $PhCO_2^-$). This material is available free of charge via the Internet at http://pubs.acs.org.

JO050246S

(21) Zimmerman, H. E. *Mol. Photochem.* **1971**, *3*, 281−92.
(22) Hatchard, C. G.; Parker, C. A. *Proc. R. Soc. London* **1956**, *235*, 518−36.